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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/460,186	06/02/1995	REID VON BORSTEL	1331-138	5103

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/460,186	VON BORSTEL ET AL.	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,18,20,22,24 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,18,20,22,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted February 26, 2009 wherein claims 1, 18, 20, 22, 24, and 25 are amended and claims 5-16, 21, and 23 are cancelled. This application is a divisional application of US application 08/176485, now US patent 5736531, filed December 30, 1993, which is a continuation in part of US application 08/061381, now abandoned, filed May 15, 1993, which is a continuation in part of US application 07/903107, filed June 25, 1992, now abandoned, which is a continuation in part of US application 07/724340, now abandoned, filed July 5, 1991, which is a continuation in part of US applications 07/438493, now abandoned, filed June 26, 1990, and 07/487984, now abandoned, filed February 5, 1990, both of which are continuations in part of US applications 07/115929 and 07/115923 respectively, now abandoned, both filed October 28, 1987.

Claims 1, 3, 4, 18, 20, 22, 24, and 25 are pending in this application.

Claims 1, 3, 4, 18, 20, 22, 24, and 25 as amended are examined on the merits herein.

Priority

Parent applications 07/438493, 07/487984, 07/115929, and 07/115923, to which priority is claimed, fail to provide adequate written description for any of the instant claims. Specifically, while these parent applications teach various acylated uridine and cytidine derivatives, they do not teach a method of using these derivatives for treating toxicity due to **a pyrimidine nucleoside analog**, much less the specific pyrimidine

nucleoside analogs recited in the dependent claims. Furthermore they also fail to disclose coadministering these compounds with inhibitors of uridine phosphorylase, cytidine deaminase, or nucleoside transport.

In addition, the parent application 07/724340 fails to provide written description for the subject of claims 1, 3, 4, 18, 20, 22, 24, and 25 namely a method of treating toxicity due to an antimalarial agent such as 5-fluoroorotate.

Therefore the effective filing date of the claims 1, 3, 4, 18, 20, 22, 24, and 25 is seen to be the filing date of parent application 07/903107, June 25, 1992.

Applicant's amendment, submitted February 26, 2009, with respect to the rejection of instant claim 11 under 35 USC 112, first paragraph, for lacking enablement for prodrugs of 5-fluorouracil or 5-fluorouridine, has bee fully considered and found to be persuasive to remove the rejection as claim 11 has been cancelled. Therefore the rejection is withdrawn.

Applicant's amendment, submitted February 26, 2009, with respect to the rejection of instant claims 1, 3-10, 14-16, 18, and 20-25 under 35 USC 112, second paragraph, for reciting the indefinite term, "pyrimidine nucleoside analog," has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to recite certain specific pyrimidine nucleoside analogs that are clearly defined. Therefore the rejection is withdrawn.

Applicant's amendment, submitted February 26, 2009, with respect to the rejection of instant claims 20, 22, 24, and 25 under 35 USC 112, first paragraph, for lacking enablement for all possible uridine phosphorylase inhibitors, cytidine deaminase inhibitors, nucleoside transport inhibitors, enhancers of hematapoiesis, and enhancers of uptake of nucleosides, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to recite certain specific compounds of these types. Therefore the rejection is withdrawn.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 18, 20, 22, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating certain specific toxicities such as damage to hematapoietic or mucosal tissue, neutropenia, reduced immune function, and opportunistic infections as discussed in the specification, does not reasonably provide enablement for treatment of all possible toxicities arising from administration of pyrimidine analogs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method for treating toxicity due to one therapeutic agent by administering a second agent. In order for the claimed methods to be enabled, one skilled in the art must reasonably be able to practice the claimed invention over the full scope of the broad genus recited in the claims, namely toxicity due to a pyrimidine nucleoside analog.

The state of the prior art: Pyrimidine nucleoside analogs are known in the art to produce a number of adverse effects. For example, the Merck manual of Diagnosis and Therapy (reference included with PTO-892) discloses that the antineoplastic pyrimidine analogs 5-fluorouracil, cytarabine (arabinosyl cytosine) and Gemcitabine produce toxic effects including myelosuppression, alopecia, mucositis, diarrhea, vomiting, hyperpigmentation, cerebellar and conjunctival toxicity. (p. 990 table 144-2). While various therapies for symptomatic relief such as antiemetics, serotonin receptor antagonists, antidopaminergics, metoclopramide, dronabinol, blood transfusions, antibiotics, granulocyte colony stimulating factor, analgesics, bland diet, and enteral

nutrition are known in the art to ameliorate specific symptoms of chemotherapy, (pp. 994-995) there is no known treatment that broadly treats all adverse effects of chemotherapeutic drugs such as 5-fluorouracil. Similarly, antiviral pyrimidine analogs such as zidovudine, (AZT) didanosine, (ddI) zalcitabine, (ddC), stavudine (D4T), and lamivudine (3TC) produce a wide variety of side effects including headache, fingernail discoloration, anemia, neutropenia, nausea, gastrointestinal upset, hepatitis, myositis, peripheral neuropathy, diarrhea, oral ulcers (mucositis), rash, and fever. (pp. 1132 right column last paragraph - p. 1133 right column second paragraph) Additionally, US patent 6992072 (cited in PTO-892) discloses that nucleoside reverse transcriptase inhibitors, for example AZT, produce side effects including lipodystrophy, changes in the sperm, osteopenia, liver damage, hyperlacticemia, lactic acidosis, pancreatitis, disorders of kidney function, diminished aerobic endurance, and weakening of the immune system. (column 3 lines 10-22) Again, no single therapy is seen to be useful for treating all of these many symptoms.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Biological systems are very complex, and changes to one pathway can have a number of different unpredictable effects. This is especially true for drugs such as nucleoside analogs which affect nucleic acid synthesis, a pathway that is essential to a wide variety of different tissues throughout the body. Given that the state of the art for the treatment of these toxicities is symptomatic management, the task of managing all of the possible symptoms of a nucleoside reverse transcriptase inhibitor would be a complex and unpredictable task

involving the administration of a number of different therapies rather than simply one single therapy.

The Breadth of the claims: The claimed invention is very broad, encompassing methods for treating any adverse effect whatsoever that results from administration of a pyrimidine nucleoside analog.

The amount of direction or guidance presented: Applicant's specification (pp. 40-42) discloses treatment of certain specific toxicities related to pyrimidine nucleoside analogs, specifically hematopoiesis, immune suppression, loss of blood cell counts, bone marrow damage, damage to gastrointestinal epithelium, opportunistic infections, and neutropenia. The specification does not disclose methods for treating all possible toxicities of pyrimidine nucleoside analogs, for example all of those listed above under the heading state of the prior art.

The presence or absence of working examples: The specification discloses animal experiments that demonstrate the effectiveness of the claimed uridine or cytidine precursors for treating hematological side effects of pyrimidine nucleoside analogs and for reducing mortality produced by these compounds. The specification does not provide working examples for methods of treating non-hematological side effects of pyrimidine nucleoside analogs.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the broad spectrum treatment of wide ranges of biological effects. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention for the full scope of the invention, one skilled in the art would have to develop novel therapeutic methods for treating a wide variety of different toxicities as discussed above. In the absence of any clear disclosure in Applicant's specification or in the prior art of a universally effective therapy, these therapies would have to be developed individually for each particular symptom of toxicity. There would be no expectation that one single therapeutic method would somehow be able to treat all possible toxicities. Thus carrying out the invention would require an undue burden of unpredictable research.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of all possible pyrimidine analog toxicities.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
6/16/2009